Developing an Agenda for Translational Studies of Resilience and Vulnerability Following Trauma Exposure

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ABSTRACT: Here we outline a translational research agenda for studies of resilience, defined as the process of adapting well in the face of adversity or trauma. We argue that an individual differences approach to the study of resilience, in which the full range of behavioral and biological responses to stress exposure is examined can be applied across human samples (e.g., people who have developed psychopathology versus those who have not; people who have been exposed to trauma versus those who have not) and even, in some cases, across species. We delineate important psychological resilience-related factors including positive affectivity and optimism, cognitive flexibility, coping, social support, emotion regulation, and mastery. Key brain regions associated with stress-related psychopathology have been identified with animal models of fear (e.g., extinction and fear conditioning; memory reconsolidation) and we describe how these regions can be studied in humans using neuroimaging technology. Finally, we cite recent research identifying neuroendocrine markers of resilience and recovery in humans (e.g., neuropeptide Y [NPY], dehydroepiandrosterone [DHEA]) that can also be measured, in some cases, in other species. That exposure to adversity or trauma does not necessarily lead to impairment and the development of psychopathology in all people is an important observation. Understanding why this is so will provide clues for the development of therapeutic interventions for those people who do develop stress-related psychopathology, or even for the prevention of adverse outcomes.

KEYWORDS: resilience; PTSD; trauma; translational research; brain; neuroendocrine markers

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DEFINING RESILIENCE

Resilience has been defined as the process of adapting well in the face of adversity, trauma, tragedy, threats of harm, or even significant sources of stress.[1] Psychological resilience can be viewed as a relatively stable constitutional resource characterized by the ability to bounce back from negative experience, or even significant adversity, by flexible adaptation to the ever-changing demands of life.[2–5] That adversity need not necessarily result in poor outcomes is an extremely important observation from a mental health perspective, since exposure to such life events is so often linked with negative consequences, including psychopathology. Accordingly, delineating the mechanisms associated with resilience constitutes an important priority for clinical neuroscientists as these studies will provide an understanding of the mechanisms underlying diverse outcomes following exposure to stress, and suggestions about how negative consequences might be neutralized or overcome.

Despite the interest in resilience, it has been difficult to validate this construct in humans using prospective studies (i.e., to determine whether those who are "resilient" would have better outcomes in response to adversity). In part, this difficulty results from the fact that definitions of resilience have not been operationalized to the extent that they can be used to determine why one person will succumb to distress or impairment when exposed to negative life events while another person will not, but this is one major goal of resilience-related research. To date, a major gap in our knowledge concerns the extent to which psychological constructs associated with resilience are altered by stress exposure, or rather, are predictors of initial response to stress exposure or the ability to achieve recovery. Indeed, are resilient people born or made?

CONCEPTUAL ORIGINS OF RESILIENCE-RELATED RESEARCH: INDIVIDUAL DIFFERENCES IN THE RESPONSE TO STRESS

It is inarguable that the primary conceptual antecedents for resilience-related research are derived from studies delineating the biological underpinnings of individual differences in the response to stress. Resilience-related research extends prior translational approaches aimed at examining the contribution of stress exposure to the development of mental illness. Indeed, historically, such studies have been interested in the effects of "stress," and have implicitly considered adverse life events and/or responses to such events, to be potent elicitors, if not etiologic agents, of mental illness. This approach has been consistent with the biopsychosocial model of mental illness and has allowed the field of clinical neuroscience to define relevant circuits or systems that might be involved in psychopathology.[6] Yet at the same time, the approach of examining homogenous effects of a stressor has fallen short of explaining

how stress actually contributes to mental illness. While it is clearly the case that many persons with mental illness have also been exposed to adverse life events, many who are exposed to similar levels of adversity do not develop psychopathology.[7] Classic studies using models of stress do not explain the variation in phenotypes; yet it is precisely the nature of these differences that might explain why some people develop stress-related psychopathology while others do not.

THE ROLE OF EARLY LIFE STRESS IN PROMOTING RESILIENCE

The complexity of the relationship between stress exposure and psychopathology can be further illustrated by considering that not only does exposure to stressful life events sometimes fail to contribute to psychopathology, but that depending on the timing and intensity of the exposure(s), it may actually be protective or "inoculating." Thus, an approach to the study of resilience ideally includes an examination of the bidirectional effects of stress. This has been difficult to achieve in animal models, but a notable exception is the study of stress-inoculated animals,[8,9] generated through the presentation of repeated maternal separations during early development. This work greatly expands the scope of resilience-related research since it is insufficient to simply argue that the effects of stress range from detrimental to neutral, but rather, that for some people, there may be benefits associated with certain types of experiences. Interestingly, the idea that stressful experiences appear to be inoculating has served as the basis for numerous training regimens in the military designed to make individuals more capable of handling stress. This has been particularly evident in recent investigations of the U.S. Special Forces and the Vietnam veteran prisoners of war by Charney, Morgan, and Southwick. In studies of these highly resilient men, early life stressors that were controllable were associated with mastery, and challenging training regimens (survival courses) served to improve stress resilience.[10]

THE RELATIONSHIP BETWEEN RESILIENCE AND STRESS-RELATED PSYCHOPATHOLOGY: THEORETICAL MODELS

Two essential theoretical models of the relationship between resilience and stress-related psychopathology can be proposed. The first model posits that putative resilience factors are protective in the face of challenge or adversity, by contributing to resistance to the development of mental illness. Thus, the absence of such factors might lead to stress-related psychopathology. It would be expected that such factors would be present as traits even in a sample of

nonexposed persons, but would be significantly more likely to be present in trauma-exposed persons who do not develop stress-related psychopathology. To the extent that these factors can be acquired, they may not be observable among persons who have posttraumatic stress disorder (PTSD), but may emerge in those who recover (e.g., following treatment). This model further implies that these factors are not associated with protection from trauma exposure. The second model proposes that resilience-related characteristics develop in reaction to environmental challenge such that the need to cope with adversity mobilizes psychological mechanisms that are likely to result in better adaptation in much the same way as biological neural defensive strategies allow short-term fight-or-flight responses while also ensuring protection from long-term damage that might otherwise be associated with such responses. This model suggests that resilience-related characteristics may only be present following exposure, or, implicitly, that the presence of a stressor will alter relationships among and between psychological and biological variables associated with resilience such that these relationships will only be apparent in response to trauma exposure.

Differentiating among these possibilities in humans requires assessment of multiple resilience-related psychological parameters and trauma exposure history in samples that include those with and without stress-related psychopathology. The concurrent examination of multiple biological measures further permits the identification of potential biological contributors to resilience-related responses. As an added level of analysis, biological variables that are associated with putatively adaptive responses to stress can also be evaluated in animals and humans. By obtaining at least some parallel biological assessments across species we can develop some assurance as to the critical biological correlates of resilience. In this way, research with animal models of fear and stress-related psychopathology (e.g., extinction and fear conditioning; memory reconsolidation) can inform and will be informed by parallel research in humans. Moreover, this understanding can be refined with the aim of understanding aspects of resilience that can be learned (i.e., or taught) in the service of helping people cope with adversity or in the service of amelioration of short- or long-term trauma-associated symptoms, or of prevention of symptom development.

DIFFERENTIATING BETWEEN RESISTANCE AND RECOVERY

In developing an agenda for psychological, biological, and ultimately, translational studies of resilience, it is essential to differentiate between two aspects of resilience—resistance and recovery—that must be evaluated separately. "Resistance" refers to psychological and/or biological characteristics that may be associated with being relatively impervious to the deleterious effects of stress. In humans, for example, this would be characterized by a failure to develop posttraumatic or other forms of psychopathology following exposure

to extreme adversity, such as sexual victimization, or even to more universal distressing events, such as bereavement. "Recovery" on the other hand, would be characterized by an individual's ability to mend or restore psychological and/or physical damage that may have resulted from trauma exposure. It is imperative not only to distinguish between distinct resilience-related prototypes, but optimally, to test the extent to which these constructs are related by comparing biological and psychological parameters and their associations in distinct trauma survivors who never developed PTSD and those who recovered from it in response to psychotherapy.

THE ROLE OF STRESS IN RESILIENCE-RELATED RESEARCH

The ultimate goal of translational studies in this field is to determine the extent to which resilience-related psychological and biological characteristics are related. This can be accomplished using statistical and inferential methodologies to provide insight into whether stressful experiences are more likely to affect stress-related measures or predict them. As an added layer of analysis, it is possible to examine similar biological and behavioral constructs in laboratory rats and nonhuman primates subdivided on the basis of behavioral phenotypes that might represent analogous prototypes of "resilience" in humans (e.g., low versus high fear responders; quick versus slow to extinction). The ability to link and compare behavioral and/or psychological responses to biological parameters in both animals and humans can provide an essential vehicle for the translational studies, critical to the ultimate identification of neural pathways.

APPROACHES TO THE TRANSLATIONAL STUDY OF RESILIENCE

The study of resilience can be accomplished through an examination of individual differences in both preexisting characteristics that predict responses to adversity, and the biological and/or behavioral concomitants of the diverse responses themselves. One strategy is to identify the range of pertinent characteristics and/or responses to adversity, and compare those at the extreme ends of the spectrum (e.g., those who are most versus least adversely affected). Relationships among variables at the ends of the extreme can then be compared and contrasted. A further comparison involves that between exposed and unexposed subjects. This approach permits a determination of whether biological and psychological differences that might be present in the extreme phenotypes reflect responses to events, or rather, factors that determine responses, such as stress resistance, recovery, or vulnerability. The strength of these two approaches can be maximized by measuring well-defined resilience-related behavioral and clinical constructs and relating them to relevant neuroanatomical,

physiological, and neurochemical markers in humans. Ultimately, many of these same biological markers can be examined in animal analogues of these resilience-related phenotypes that are created via standardized experimental procedures (e.g., stress inoculation, fear extinction, memory consolidation, and reconsolidation).

By elucidating the individual differences, detectible before, during, or after stress exposure, that serve to modulate responses to stress or trauma, it is possible to ultimately determine whether these differences can be manipulated so as to result in different outcomes (e.g., can phenotypic differences associated with vulnerability be reversed?). Accordingly, an analysis of individual differences in behavioral response to stress and their concomitant neurobiological underpinnings in animals is an essential first step toward understanding the salient qualities associated with human resilience.

RELEVANT PSYCHOLOGICAL CONSTRUCTS ASSOCIATED WITH RESILIENCE

We delineate critical elements associated with resilience, including positive affectivity and optimism, cognitive flexibility, coping, including religious coping, social support and intimacy, emotion regulation, and mastery. We provide definitions of these constructs and cite relevant literature below but space limitations preclude an exhaustive review of the literature.

Positive affectivity refers to the trait of being joyful, interested, and contented in life. That this trait is associated with resilience is supported by findings showing that positive affectivity decreases autonomic arousal and facilitates positive reappraisal.[11] Although positive affect can be measured as a stable personality trait, it is also possible to measure mood as a state and to consider the extent to which resilience-related positive affectivity is trait or state related. Optimism is related to positive affect and may be related to resilience as evidenced by findings showing that optimists tend to use more adaptive coping strategies, such as positive reinterpretation and growth, and seek out supportive personal relationships during life transitions and crises.[12] Additionally, optimism predicts better psychological responses to breast cancer diagnosis[13] and lower likelihood for rehospitalization after coronary artery bypass graft surgery.[14]

Cognitive flexibility is exemplified by positive reframing, or reappraisal, and refers to the ability to reinterpret an adverse or negative event so as to find meaning and opportunity. This characteristic has been related to decreased likelihood of developing PTSD in combat veterans,[15] better adjustment after loss of a family member,[16] reductions in plasma cortisol among women with early stages of breast cancer[17] and better adjustment after surviving a natural disaster.[18]

Active coping strategies have been associated with the ability to manage stressful situations, fewer psychological symptoms, and improved well-being

among at-risk children,[19] college students,[20] traumatized and depressed adults,[21] and patients with a variety of medical conditions.[22] Active coping strategies have been associated with reduced stress-related symptoms in Gulf War veterans.[23] More recently, lower levels of distress and PTSD 6 months after 9/11 were found among individuals who engaged in active coping compared to those who used passive coping strategies (e.g., denial, giving up).[24]

Another form of coping that may be effective in the face of adversity is religious coping, which has been associated with better psychological adjustment in patients facing kidney transplant surgery and their caregivers,[25] hospitalized older adults,[26] and people exposed to flood.[27] Potential mechanisms linking religion/spirituality to better mental and physical health (including measures of cardiovascular, neuroendocrine, and immune system functioning) include the use of meditation practices or prayer, having a motivational or orienting force for living (e.g., meaning), or though the supportive functions of belonging to a religious group and/or a feeling of closeness to God or a higher spiritual being.[28–30]

Social support involves perceived availability of supportive functions, including tangible forms of support (e.g., someone who would provide an emergency loan or a ride to the airport) as well as love, attachment, and intimacy or what Ryff and Singer[31] refer to as "interpersonal flourishing" and aspects of social integration (e.g., frequency of contact with family, friends, and participation in social and, as noted above, religious groups). Both aspects of social support are, associated with physical and psychological well-being and resilience to diverse health outcomes,[32,33] as well as measures of cardiovascular, neuroendocrine, and immunological functioning.[31,34,35] Social support is also associated with better psychological outcomes among people exposed to trauma including a ship disaster[36] and childhood sexual abuse.[37]

The ability to regulate negative emotion, including the capacity to decrease the duration of negative affect once it begins may be protective against adverse reactions to stress or trauma exposure, but this has not yet been systematically studied. Yet, as described below, emotion regulation has been linked to the same brain areas associated with PTSD.

Mastery refers to an individual's belief that he or she can solve life's problems, and/or respond effectively in the face of stress.[38] Loss of a sense of mastery over time is associated with depressed mood and anger among inner city women.[39] Low sense of mastery (and avoidance of coping strategies) are associated with the development of anxiety disorders among family caregivers of heart transplant patients[40] and with more physical symptoms and impairment among transplant patients.[41]

Arguably, these characteristics can reflect preexisting traits. What is not known is the degree to which these factors are related to one another, largely because although they are at times studied together in the same population (e.g., coping, social support, etc.), it is not known to what extent these features are distinct. Thus, it is critically important to examine whether these different

constructs indeed reflect a common underlying factor that is resilience, or rather distinct aspects that are each necessary components of resilience. It is also necessary to determine the extent to which these characteristics foretell responses to life events or, rather are modified by them. For example, some protective factors may be "risk-activated moderating factors"[42] only becoming fully activated when the individual is challenged (e.g., effective parenting strategies, coping skills). Furthermore, some characteristics may be more important than others, or may be able to compensate for deficits in other characteristics, thus ultimately, these factors, or lack of them, must be evaluated with respect to their relative contributions to the prediction of who will suffer adverse outcomes in response to stress, and who will recover more readily.

RELEVANT BIOLOGICAL CONSTRUCTS ASSOCIATED WITH RESILIENCE

The Centrality of the Amygdala and mPFC to Studies of Resilience

Animal studies have shown that the lateral nucleus of the amygdala integrates and forms an associative link between unconditioned and conditioned fear stimuli. The lateral nucleus communicates with the central nucleus of the amygdala, which then connects to hypothalamic and brainstem regions that control the specific expression of fear responses.[43] This work has formed the basis for the neuroimaging studies of patients with anxiety disorders, who demonstrate abnormalities in fear conditioning and extinction, and associated neural circuits and neuromodulators. A variety of studies have demonstrated evidence of amygdala hyperresponsiveness in anxiety disorders, such as PTSD. These studies now set the stage to study amygdala responsiveness in relation to resilience. A detailed review of findings relating to the amygdala and medial prefrontal cortex (mPFC) in anxiety disorders is presented in Liberzon,[44] and Shin.[45]

It can be easily hypothesized that resilience-related traits or phenotypes would be associated with less amygdala activation and more mPFC activation in response to tasks designated to evaluate these brain structures, however, the impact of trauma exposure and/or recovery has not yet been examined.

Yet, insofar as amygdala and mPFC activation are altered in PTSD, it is reasonable to hypothesize that these phenomena may be responsive to intervention, such as psychotherapy. After all, prolonged exposure therapy, used in the treatment of PTSD, may be based, in part, upon the process of extinction. In fact, the ability to extinguish the conditioned fear response may be a key element that distinguishes individual vulnerability to stress. LeDoux and colleagues review prior work by their group and others demonstrating that lesions of mPFC impair extinction, essentially converting extinguishable fear into extinction resilient fear.[46] These findings suggest that abnormalities in mPFC will

relate to chronic fear states whereas robust mPFC function relates to resilience. LeDoux and colleagues[43,47] have also recently provided evidence that mPFC activation in humans is directly related to extinction. Indeed, Phelps *et al*.[48] have recently demonstrated that fear extinction in the human brain involves two mPFC regions (ventral infralimbic and prelimbic areas; dorsal–anterior cingulate) that may correspond to rodent work. A related phenomenon under active investigation is memory reconsolidation. For many years, it commonly has been believed that "consolidated" memories, or memories that had been transferred to long-term storage were not subject to modification. Results from recent studies with rodents,[49–51] however, have led to renewed and intense interest in the reconsolidation hypothesis. This model posits that when a previously consolidated memory is recalled, it enters a highly labile state prior to being returned to long-term storage (i.e., reconsolidated).[52] Although there is limited evidence to support memory reconsolidation in humans, an implication for intervention is that there may be a window of opportunity for modifying traumatic memories when recalled in a therapeutic setting, that is, before they are reconsolidated.[53,54] These findings demonstrate the feasibility of translational work with respect to these neural circuits and behavioral concomitants across species.

In humans, the activity of the amygdala and mPFC can be measured in response to different types of provocation, which may be associated with different aspects of resilience. For illustration, we describe three tasks/processes that may be important for the evaluation of resilience-related circuitry. First, it is possible to test one's ability to regulate a negative emotional response to an upsetting picture through cognitive reappraisal. Persons who are able to willfully manipulate their emotional response appear to do so through a deliberate conscious cognitive transformation of emotional experience, in which they can mobilize an ability to think about the stressful event in a new way. This process has been associated with reduced amygdala and increased mPFC activation. A second kind of provocation is the Threat of Shock paradigm in which subjects do not actually receive a shock, but are instructed that they may receive one under specific conditions, thus generating "anticipatory anxiety."[55,56] It would be of interest to examine whether and to what extent reduced amygdala activation or increased mPFC responses to this paradigm correlate with neural activity measured during the aforementioned emotion regulation paradigm. Similarly, the amygdala reactivity that is associated with habituation to fearful faces (a third provocation) may or may not be correlated to neural activity in the other two tasks, even though they involve activation of the same brain areas.

To the extent that we learn that different provocations produce similar brain perturbations, this will support the identification of a final common pathway with respect to resilience. However, it may be the case that differences in brain activation patterns result from different tasks. The latter result would support the idea that neural circuits are related to circumscribed resilience-related behaviors (as opposed to a broader range of traits consistent with resilience).

Here too, there would be opportunity for follow-up in determining whether the paradigms that generate different functional neuroanatomical responses correlate differently with other biological or psychological measures.

Resilience-Related Neurochemical Measures

Several compounds have recently been hypothesized as being related to resilience.[1] Neuropeptide Y (NPY) is a peptide with behaviorally relevant effects on the hippocampus and is thought to function as an anxiolytic.[57,58] There are important functional interactions between NPY and corticotropin-releasing hormone (CRH) such that NPY counteracts the anxiogenic effects of CRH.[57,59] NPY also has counterregulatory effects on norepinephrine (NE) in many brain areas associated with anxiety, fear, and depression.[60–63] Preliminary studies have demonstrated that persons under extreme stress with high NPY levels show better performance than those with low levels of NPY.[64] Similarly, patients with PTSD have reduced baseline plasma NPY levels and a blunted yohimbine-induced NPY increase.[65] While there is increasing enthusiasm to learn more about this measure, there is no basis for predicting whether this would be a trait or state measure. Recently, a significant group difference in plasma NPY was observed, reflecting higher NPY levels in exposed veterans without PTSD than in nonexposed, but comparable levels in veterans with current PTSD.[66] Among those without current PTSD, veterans with past PTSD, had higher NPY levels than those without past PTSD. NPY levels were significantly predicted by extent of symptom improvement and lower combat exposure, and significant at a trend level, with positive coping. These findings support the idea that plasma NPY levels may represent a biological correlate of resilience to, and/or recovery from, the adverse effects of stress.

Another putative marker of resilience may be dehydroepiandrosterone (DHEA), and/or the ratio of DHEA with cortisol. Morgan and Charney[67] found a positive correlation between elevations in DHEA (and the DHEA/cortisol ratio) and the ability to perform well under conditions of acute stress—DHEA/cortisol ratios were indeed higher in military trainees who performed well during extreme stress compared to those who did not. Like cortisol, DHEA is an endogenous hormone secreted by the adrenal gland in response to adrenocorticotropic hormone (ACTH), but is the product of 17-hydroxypregnenolone, rather than 17-hydroxyprogesterone. Alterations in the balance of adrenal steroids imply changes in metabolism, some of which can certainly be associated with protective factors, or biochemical processes associated with PTSD. Results of studies examining DHEA or dehydroepiandrosterone sulfate (DHEAS) levels in PTSD, however, have been mixed with some reporting increased concentrations of DHEA,[68–70] some showing reduced levels,[71] and others failing to demonstrate any alterations in PTSD compared to controls.[72]

It has been proposed by some clinical investigators that elevations in

peripheral levels of DHEA and DHEAS in PTSD contribute to the decrease in basal circulating cortisol levels and other alterations of the hypothalamic-pituitary-adrenal (HPA) axis than have been reported.[68] Related to this, on the basis of examination of soldiers showing more positive outcomes in response to the extreme stress of military survival training in relation to DHEAS levels,[67] it has been recently suggested that DHEA may have ameliorative properties in promoting recovery from the effects of trauma.[1] But it can just as easily be argued by those showing reductions in DHEA that in PTSD, the absence of these metabolites may facilitate increased glucocorticoid sensitivity. Since the DHEA/cortisol ratio was found to correlate with symptom severity, it is plausible that this constitutes to be a state-related resilience measure that will be manifest following successful treatment, but not be present prior to treatment. Increased in DHEA/cortisol ratio in responders may also be associated with a "normalization" in cortisol hypersuppression.

A recent study showed that although combat veterans with PTSD showed significantly higher plasma DHEA, regression analysis demonstrated that DHEA and DHEAS levels were related to symptom improvement (and not symptom severity), implying that DHEA levels may play a role in modulating recovery from PTSD, as observed by Morgan *et al*.[61] A significantly lower cortisol/DHEA ratio controlling for age, which, in contrast, was predicted by severity of childhood trauma and current symptom severity, was also observed.[73] Much of the interest in the role of DHEA in psychiatric disorder, including its putative effects on resilience and/or anti-glucocorticoid properties, is linked to DHEA's neurosteroidal action, not its peripheral effects.[74–79] Yet, peripheral levels of DHEA may be potentially informative with respect to central effects in that DHEA can cross the blood–brain barrier, and can be synthesized in brain *de novo* independent of ACTH regulation of adrenal steroidogenesis.[80] Certainly, demonstrations of anxiolytic actions,[81,82] antagonism of GABA receptor,[83] or actions at the N-methyl-D-aspartate (NMDA) receptor[84] in response to DHEA administration, reflect the brain as the physiologic target for this steroid. Insofar as there is no evidence that DHEA interacts with the glucocorticoid receptor,[85] concentrations of circulating DHEA may impact functions independently of cortisol, whether these effects are central or peripheral.

Biological Measures Thought to be Associated With Vulnerability for PTSD or PTSD Symptom Severity

Also relevant to the study of resilience are biological measures associated with vulnerability, including 24-h urinary cortisol excretion, lymphocyte glucocorticoid receptor (GR) number, and enhanced glucocorticoid responsiveness as measured by the lysozyme IC_{50}. In numerous studies, these measures have been shown to be associated with pre-traumatic risk factors, such

as age of traumatization (with earlier trauma being associated with greater responsiveness) and parental PTSD. The idea that basal cortisol represents a stable, trait-related characteristic is also supported by the finding of elevated cortisol levels in first-degree relatives of depressed patients,[86] the finding of relatively stable urine cortisol levels collected for 21 consecutive days,[87] the high concordance between cortisol levels in monozygotic twins,[88] and the relatively small variance in total cortisol output associated with situational factors, like stress.[89]

Measures that may be more associated with PTSD symptom severity are 24-h urinary NE excretion, circadian rhythm of cortisol, and enhanced negative feedback inhibition, as reflected by the cortisol response to dexamethasone (DEX). The basis for the hypothesis that catecholamine levels are related to symptom severity come from studies demonstrating that Vietnam veterans with PTSD show higher plasma NE and 3-methoxy, 5-hydroxyphenol glycol (MHPG) levels at baseline,[90] and following neuroendocrine provocation compared to nonpsychiatric controls.[91] That circadian rhythm of cortisol may be related to symptom severity is supported by the relationship between circadian rhythm and psychological variables, and stress in nonpsychiatric participants. In one study, the chronic stress of unemployment was associated with altered diurnal cycles (i.e., greater peak-to-trough differences). Changes in the diurnal pattern of cortisol excretion in the direction of a greater peak-to-trough difference appeared to be associated with state-related psychological variables, such as mood and perceived stress.[92]

Negative feedback inhibition also seems to be altered with symptom improvement,[93,94] on the basis of cross-sectional and correlational data in PTSD. However, the hypothesis that the DST is a state measure is particularly strengthened by data examining cortisol suppression to DEX in major depression. Studies of depressed patients have shown that those who are successfully treated revert back to having a normal cortisol response to DEX,[95,96] but whether this is a attributable to direct actions of antidepressants on GR[97] or is mediated by psychological variables is not clear. By measuring these parameters in nonpsychiatric, exposed, and nonexposed subjects, and longitudinally, in relation to the development and recovery from PTSD, it is possible to distinguish between measures reflecting resilience, risk, symptom severity, and recovery from trauma.

IMPLICATIONS OF RESILIENCE-RELATED RESEARCH IN THE PREVENTION AND TREATMENT OF STRESS-RELATED PSYCHOPATHOLOGY

To the extent that we can identify psychological and biological correlates of individual differences associated with resilience, we can then test for their relevance to prevention and treatment of stress-related psychopathology.

From the extensive analyses of psychological factors obtained from a large and diverse group of nonexposed, exposed and symptomatic persons, it will ultimately be possible to identify factors associated with resilience, and other domains that are not currently thought to be particularly relevant to the development of stress-related psychopathology, but that are in fact related, and may be amenable to cognitive, behavioral, or other psychological intervention. For example, qualities, such as optimism, emotion regulation, humor, or spirituality—that are not at the forefront of trauma-related psychotherapy—may be revealed in this work to be as relevant as factors, such as cognitive reappraisal and social support, which are emphasized in specialized treatment approaches.

To the extent that these psychological measures can be related to biological measures, this will enrich the observations even further. It is anticipated that new targets for prophylaxis and treatment may arise if results of functional neuroimaging coalesce toward the same neuroanatomical structures and neural circuits. This can also be anticipated for results of neurochemical and neuroendocrinological investigations.

Despite decades of research into the underpinnings of stress responses and their relationships to mental illness, clinical neuroscience has little to offer during times of national catastrophe, and to those who suffer from personal tragedy, current treatment approaches can sometimes be found lacking. Thus, there is a moral imperative to this work so that our field can offer the public tools for education and prevention by delineating strategies for resistance and recovery.

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